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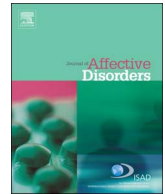
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Research paper

Associations between pain and depression in nursing home patients at different stages of dementia



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ABSTRACT

Background: Pain is associated with depression in nursing home patients with dementia. It is, however, unclear whether pain increases depression. Therefore we evaluated the prospective associations between pain and depressive symptoms in nursing home patients at different stages of cognitive impairment.

Methods: Two longitudinal studies were combined, including 931 patients (≥ 65 years) from 65 nursing homes. One study assessed patients at admission, with 6-month follow-up (2012–2014). The other study assessed residents with varying lengths of stay, with 4-month follow-up (2014–2015). Patients were assessed with the Mini-Mental State Examination, the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, and the Cornell Scale for Depression in Dementia.

Results: At baseline, 343 patients (40% of 858 assessed) had moderate to severe pain, and 347 (38% of 924) had depression. Pain increased the risk of depression (OR 2.35, 95% CI 1.76–3.12). Using mixed model analyses, we found that a 1-point increase in pain was associated with a .48 increase in depression ($p < .001$). This association persisted in mild, moderate, and severe cognitive impairment. In those recently admitted, depressive symptoms decreased over time, and having less pain at follow-up was associated with a decrease in depressive symptoms (within-subject effect; $p = .042$).

Limitations: The two cohorts had different inclusion criteria, which may reduce generalisability. The study design does not allow conclusions on causality.

Conclusions: Pain and depressive symptoms are associated in patients with dementia. Because reduced pain is associated with less depressive symptoms, these patients should be assessed regularly for untreated pain. The benefit of analgesic treatment should be weighed carefully against the potential for adverse effects.

1. Introduction

In Norway, over 80% of nursing home patients have dementia (Helvik et al., 2015). Symptoms of depression affect up to 50% of people with dementia, causing increased suffering, reduced quality of life, and possibly shortened life expectancy (Enache et al., 2011; Gonzalez-Salvador et al., 2000; Janzing et al., 1999; Todd et al., 2013). Depression in people with dementia may also accelerate the decline in daily functioning and cognition, and contribute to the loss of independence and earlier nursing home placement (Luppa et al., 2008;

Potter and Steffens, 2007; Rapp et al., 2011). Over time, depression often persists and re-occurs in these individuals (Selbaek and Engedal, 2012; Selbaek et al., 2013), and may be associated with worse outcomes of medical treatment (Bellelli et al., 2008; Lenze et al., 2007; Smith et al., 2015).

To manage mild to moderate depression in people with dementia, nonpharmacological interventions such as psychotherapy, reminiscence therapy, and personalized pleasant activities are recommended as first-line treatment (Kales et al., 2015; Orgeta et al., 2015; Testad et al., 2014). In severe depression, pharmacological treatment with antide-

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pressants is recommended, although updated systematic reviews of the use of antidepressants for depression in people with dementia did not find conclusive evidence for efficacy in this population (Leong, 2014; Nelson and Devanand, 2011).

Thus far, little attention has been paid to potential modifiable causal factors of depression such as untreated chronic pain. Approximately 40–60% of nursing home patients are suggested to be in daily moderate to severe pain (Achterberg et al., 2010; Husebo et al., 2011). People with dementia are at particular risk of untreated pain because their ability to understand, evaluate, and verbally communicate symptom severity gradually decreases (Flo et al., 2014). This may trigger symptoms such as depression, agitation, and sleep problems (Ballard et al., 2009). The interrelationship between pain and depression, known as the “pain-depression dyad”, is well documented in people *without* dementia (Bair et al., 2003; Goldenberg, 2010). Although no clear aetiology has been established, the conditions are known to commonly coexist, mutually exacerbate each other, share common signal pathways and neurotransmitters, and respond to similar treatments (Chopra and Arora, 2014).

The pain-depression dyad is not sufficiently investigated in people *with* dementia (Bair et al., 2003; Goldenberg, 2010). Thus far, four cross-sectional studies have found a significant association between pain and depression in nursing home patients with moderate to severe dementia (Cipher and Clifford, 2004; Leong and Nuo, 2007; Malara et al., 2016; Williams et al., 2005), including one study which also reported the prevalence of pain and depression stratified by cognitive status (Leong and Nuo, 2007). The most recent study by Malara et al. (2016) included 233 patients at different stages of dementia and found a significant association between pain and depression as evaluated by a physician. Although these studies provide important insights, some had a low sample size, did not assess pain and/or depression with validated proxy-rated instruments, and all studies lack prospective data to evaluate whether pain is associated with future worsening of depression. In the current study, we investigate the prospective associations between pain and depression in nursing home patients with advanced dementia to explore whether pain may be an exacerbating factor for depression, or vice versa. We addressed the following research questions: i) Is the intensity of pain associated with the severity of depression? ii) Is change in pain over time associated with change in depression? iii) How are these associations affected by cognitive function and use of analgesic or antidepressant drugs?

2. Methods

2.1. Sample

We analysed prospective data from two independent multicentre studies in 6 counties of Norway. The REDIC (*RE*source Use and *DI*sease Course in Dementia) study included all patients aged ≥ 65 years (or younger, if established dementia diagnosis) at admission to nursing home care with an expected stay of > 4 weeks, and life expectancy > 6 weeks, from January 2012 to June 2014 (Sandvik et al., 2016a). In total, 696 patients were included from 47 nursing homes. The current analyses use data collected at month 0 and 6, excluding 12 patients aged < 65 years (Fig. 1). The other study, COSMOS (COmmunication, Systematic pain treatment, Medication review, Organized activities and Safety), included all patients aged ≥ 65 years in long-term nursing home care, excluding patients with diagnosis of schizophrenia or life expectancy < 6 months, from April 2014 to June 2015 (Husebo et al., 2015). In total, 545 patients were included from 67 units (clusters) in 31 nursing homes. Clusters were randomised to receive either a complex intervention or care as usual (Husebo et al., 2015). The current analyses use data from the control group, comprising 247 patients from 26 units, collected at month 0 and 4 (Fig. 1).

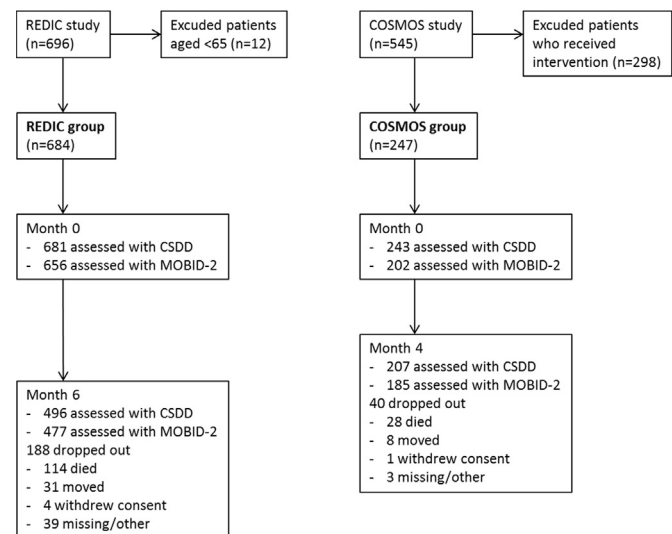


Fig. 1. Patients included in the final analyses.

2.2. Data collection

Data collection in both studies was completed in close collaboration with a staff member who had been familiar with the patients for a minimum of 4 weeks prior to data collection. The staff received training in the appropriate use of each outcome measure (Table 1), and had assistance from the researchers as needed. Demographic information and scheduled drug prescriptions (excluding prescriptions given “as needed”) were extracted from the patients’ medical records. Analgesic use at baseline and follow-up was assessed by counting the number of prescriptions for drugs classified as systemic analgesics (Anatomical Therapeutic Chemical (ATC) code N02 or M01A) at each time point. Similarly, antidepressant use was assessed by counting the number of prescriptions for drugs classified as antidepressants (ATC code N06A) at baseline and follow-up. We did not assess the appropriateness of dose; i.e. a dose adjustment from baseline to follow-up was not registered.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE), with scores from 26 to 30 defined as no/questionable, 21–25 as mild, 11–20 as moderate and 0–10 as severe cognitive impairment (Folstein et al., 1975; Perneczky et al., 2006). Pain was assessed using the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale, with moderate to severe pain defined as a score of ≥ 3 (Husebo et al., 2014). Depressive symptoms were assessed using the Cornell Scale for Depression in Dementia (CSDD), and depression defined as a score of ≥ 8 (Alexopoulos et al., 1988; Burns et al., 2004). The Neuropsychiatric Inventory – Nursing Home version (NPI-NH) was used to assess neuropsychiatric symptoms (Cummings et al., 1994; Selbaek et al., 2008), and the NPI-depression subscale was used as a secondary outcome measure.

2.3. Statistical analysis

Baseline characteristics were described with mean and standard deviation (SD) for continuous variables and with number of patients and percentages of sample size for categorical variables. Differences at baseline between the studies were tested with independent samples *t*-tests for normally distributed continuous variables, Mann-Whitney *U*-test for non-normal distributed continuous variables and Pearson χ^2 tests for categorical variables. The unadjusted odds ratio (OR) for depression among patients with moderate to severe pain was calculated at baseline. Linear regression models were fitted to analyse the prospective association between pain at baseline and depression at follow-up, and vice versa, adjusted for depression, pain, age, sex, and cognitive function at baseline. To account for intra-cluster correlation

Table 1
Assessment scales.

	What does the tool measure?	Tool characteristics and psychometric properties
MMSE	Staging of cognitive impairment based on scores in 8 domains (orientation to time and place, short-term recall, attention, calculation, long-term recall, language, repetition, and complex commands), questionnaire administered directly to the patient	30 items yield a sum score from severe (0–10), moderate (11–20), mild (21–25), to no cognitive impairment (26–30) (Folstein et al., 1975). Widely used as a screening tool, with good reliability and validity (Tombaugh and McIntyre, 1992).
MOBID-2 Pain Scale	Assessment of pain intensity in dementia inferred by observation of pain behaviours during standardised, guided movement (part 1 - musculoskeletal system; current) and previous observations of other pain behaviours (part 2 - internal organs, head and skin; in the last days), proxy rated	Each item is rated on a horizontal scale from 0 (no pain) to 10 (worst pain imaginable). Yields a final assessment of total pain (range 0–10) (Husebo et al., 2007). Excellent reliability and validity, good responsiveness (Husebo et al., 2014). Total pain ≥ 3 was defined as moderate to severe pain.
CSDD	Depressive symptoms in people with dementia in 5 domains (mood-related signs, behavioural disturbance, physical signs, cyclic functions, and ideational disturbance) in the last week, proxy rated	19 items with each symptom score rated from 0 (not present) to 2 (severe) (Alexopoulos et al., 1988). Satisfactory interrater reliability and validity in the elderly population (Korner et al., 2006). Sum score ≥ 8 defined as depression (Burns et al., 2004).
NPI-NH	The frequency and severity of 12 neuropsychiatric items in dementia (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, loss of inhibition, irritability/lability, aberrant motor behaviours, sleep and appetite and eating disturbances), proxy rated	The product of frequency (0–4) and severity (1–3) yields a composite score per item from 0 (not present) to 12 (most frequent and severe symptoms), with a cut-off value of ≥ 4 for clinically significant symptoms. Sum score 0–144 (Cummings et al., 1994). The Norwegian version has shown good reliability and validity (Selbaek et al., 2008).

at the nursing home level, we used robust estimators for variance. To explore whether increasing pain was associated with increasing depression, and vice versa, we used linear mixed effect models with restricted maximum likelihood estimation. We conducted several analyses for the outcome variables where we included fixed effects for MOBID-2, CSDD, time, antidepressant use, and analgesic use (time-varying covariates), and MMSE, age, and sex (time-constant variables). Associations at different stages of cognitive functioning were assessed by stratifying according to MMSE (Perneczky et al., 2006). To account for intra-cluster correlation, the models were fitted with random intercept for both nursing home and patient-level effects. We included random slope for MOBID-2 and CSDD at patient-level, thus allowing the effects of these covariates to vary between patients. The covariance structures were specified using an independent model for both patients and nursing homes. The regression coefficients for the time-varying covariates can be interpreted as a between-patients effect and/or a within-patient effect. To investigate this further, we included both within and between effects in the same model (Rabe-Hesketh and Skrondal, 2012). Mixed model analyses were also conducted using NPI-depression as a dependent variable, with MOBID-2, time, MMSE, age, and sex as independent variables, to explore whether any associations obtained using the CSDD scale were replicated. We regarded $p < .05$ as statistically significant. All analyses were conducted with Stata/IC version 14 (StataCorp LP, College Station, TX, USA).

2.4. Ethical and legal considerations

Verbal and written informed consent was obtained from the patients if they had sufficient ability to consent; if not, written presumed consent was obtained from a legally authorised representative, in accordance with the ethics committee requirements and current Norwegian legislation. The REDIC and COSMOS trials were approved by the Regional Committees for Medical and Health Research Ethics, 2011/1738 and 2013/1765, and registered at clinicaltrials.gov, NCT01920100 and NCT02238652, respectively.

3. Results

We included 931 patients with a mean age of 85.4 (SD 7.0) and mean MMSE score of 14.6 (SD 7.1); 622 (66.8%) were women (Table 2). In total, 703 completed the follow-up assessments, 142 died, 39 moved home or to a different institution/ward, 5 withdrew consent to participate, and 42 were lost to follow-up for other reasons (Fig. 1). Compared to the REDIC study, participants included in the COSMOS trial were older and had a higher ratio of women. They had lower MMSE scores, more pain and depressive symptoms, neuropsychiatric

symptoms, and used more analgesics and antidepressants. At baseline, 343 of all patients (40.0% of those who completed the assessment) had moderate to severe pain (MOBID-2 ≥ 3), 347 (37.6%) had depression (CSDD ≥ 8), and 164 (19.2% of 856 patients who completed both assessments) had both pain and depression. The unadjusted OR of patients with moderate to severe pain having depression was 2.35 (95% CI 1.76–3.12). MOBID-2 assessments at baseline and follow-up were completed by 617 patients, of whom 137 (22.2%) had moderate to severe pain at both assessments. Mean pain score was unchanged from baseline to follow-up, and 92 patients (14.9%) had new incidence moderate to severe pain at follow-up. CSDD assessments at baseline and follow-up were completed for 699 patients, of whom 144 (20.6%) had depression at both assessments, and 81 patients (11.6%) had new incidence depression at follow-up.

Using linear regression, we found that pain at baseline was significantly associated with depression at follow-up in both the REDIC and COSMOS groups (coefficients .26 and .70, $p = .022$ and $< .001$, respectively). When adjusting for covariates, this association remained significant only in the COSMOS group (Table 3). Similarly, depression at baseline was significantly associated with pain at follow-up in both groups in the unadjusted analyses (coefficients .06 and .11 for REDIC and COSMOS, respectively, $p < .001$), but only significantly in the REDIC group (coefficient .05, $p = .008$) after adjusting for covariates.

Using linear mixed model analyses, adjusted for time (months), MMSE, age, and sex, we found that patients with more pain were significantly more depressed than those with less pain, and vice versa (Model 2, Table 4). An increase of 1 on the MOBID-2 scale was associated with an increase of .48 on the CSDD scale ($p < .001$) and with an increase of .11 on the NPI-depression subscale ($p = .005$). An increase of 1 on the CSDD scale was associated with an increase of .10 on the MOBID-2 scale ($p < .001$). When measures of between- and within-subject effects were included in the model, only the between-subject effects were significant ($p < .001$ for between-, and $p = .113$ for within-subject effects). Over time, depression scores decreased in severity (.10 decrease in CSDD scores per month, $p = .007$), as opposed to pain which remained unchanged. The severity of pain and depression was gender independent (coefficients .26, $p = .069$; $-.08$, $p = .814$; respectively). Older patients had more pain (coefficient .02, $p = .014$) but less depression ($-.10$, $p < .001$), and those with more severe cognitive impairment had more depression (1 point less on the MMSE scale was associated with .12 increase in CSDD, $p < .001$), but not more pain (coefficient .00, $p = .721$). However, the progression of depression over time (Fig. 2) was not affected by MMSE score ($p = .990$). The mixed model analyses were re-calculated separately for the REDIC and COSMOS groups with unchanged results, except that the COSMOS

Table 2
Characteristics of included patients at baseline; total and between groups.

	Total (n = 931)	N ^a	REDIC (n = 684)	N ^a	COSMOS (n = 247)	N ^a	p
Age ^a	85.4 (7.0)		84.8 (6.8)		87.0 (7.2)		< .001
Female ^b	622 (66.8%)	931	437 (63.9%)	684	185 (74.9%)	247	.002
MMSE ^a	14.6 (7.1)		15.7 (6.4)		11.4 (7.9)		< .001
MMSE ≤ 20 ^b	673 (80.2%)	839	487 (78.2%)	623	186 (86.1%)	216	.012
MOBID-2 ^c	2.3 (2.3)		2.1 (2.1)		2.8 (2.8)		.008
MOBID-2 ≥ 3 ^b	343 (40.0%)	858	249 (38.0%)	656	94 (46.5%)	202	.030
CSDD ^c	6.8 (5.6)		6.5 (5.2)		7.8 (6.4)		.017
CSDD ≥ 8 ^b	347 (37.6%)	924	243 (35.7%)	681	104 (42.8%)	243	.049
NPI-NH total score ^c	14.0 (17.0)	924	12.8 (15.3)	681	17.6 (20.7)	243	.012
NPI-NH depression ^c	1.8 (3.1)	909	1.9 (3.1)	675	1.7 (3.1)	234	.448
Analgesics ^b	445 (47.8%)		288 (42.1%)		157 (63.6%)		< .001
Antidepressants ^b	292 (31.4%)		193 (28.2%)		99 (40.1%)		.001

Numbers represent mean (SD) or number of patients (%).

MMSE: Mini-Mental State Examination; NPI-NH: Neuropsychiatric Inventory-Nursing Home Version.

^a Number of patients who completed each assessment.

^b Independent-samples *t*-test.

^c Pearson χ^2 -test.

^d Mann-Whitney *U*-test.

Table 3
Linear regression; associations with pain and depression at follow-up.

Dependent variable (follow-up)	Independent variable (baseline)	REDIC (n = 453)		COSMOS (n = 158)	
		Coef.	p	Coef.	p
CSDD	MOBID-2 (unadjusted)	.26	.022 [*]	.70	< .001 [*]
CSDD	MOBID-2	.08	.358	.41	.026 [*]
	CSDD	.48	< .001 [*]	.49	< .001 [*]
	MMSE	-.04	.357	-.07	.188
	Sex	.30	.347	.32	.802
	Age	-.08	.007 [*]	.01	.818
MOBID-2		REDIC (n = 439)		COSMOS (n = 138)	
		Coef.	p	Coef.	p
	CSDD (unadjusted)	.06	< .001 [*]	.11	< .001 [*]
	CSDD	.05	.008 [*]	.06	.064
	MOBID-2	.38	< .001 [*]	.38	.005 [*]
MOBID-2	MMSE	.03	.039 [*]	-.01	.849
	Sex	.13	.531	.37	.435
	Age	.01	.395	-.01	.800

COSMOS, *Communication, Systematic pain treatment, Medication review, Organized activities and Safety* Study; CSDD, *Cornell Scale for Depression in Dementia*; MMSE, *Mini-Mental State Examination*; MOBID-2, *Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale*; REDIC, *REsource Use and Disease Course in Dementia* Study. Analyses include all patients with valid assessments at baseline and follow-up, and are adjusted for intra-cluster effects at the nursing home level.

^{*} Significant association at $p < .05$ level.

population did not have a significant reduction in depressive symptoms over time (coefficient $-.08$, $p = .474$). The REDIC population had a significant within-subject effect of pain on depressive symptoms, i.e. a patient who had reduced pain at follow-up had significantly less depressive symptoms at follow-up compared to baseline (between-subject coefficient $.62$, $p < .001$, within-subject coefficient $.23$, $p = .042$). In the COSMOS population, only the between-subject effects were significant ($p = .317$ for individual effects).

The associations between pain and depressive symptoms remained significant when use of analgesics and/or antidepressants at baseline and follow-up was included in the mixed models (Model 3–5, Table 4). Use of analgesics was significantly associated with pain and depression. A patient who received an increased number of analgesics from baseline to follow-up had significantly increased pain (coefficient $.65$, $p < .001$) and increased depression ($.49$, $p = .006$) in the same period (Model 4, Table 4). Number of prescribed antidepressants was significantly

associated with depressive symptoms (1.2 , $p < .001$), but not with pain ($-.02$, $p = .873$) (Model 3, Table 4).

When patients were grouped according to cognitive function, pain was significantly associated with increased depression in people with mild (coefficient $.47$, $p = .005$) and moderate ($.62$, $p < .001$) cognitive impairment, and near-significantly in those with severe cognitive impairment ($.24$, $p = .050$; Table 5), but not significantly associated in those with no/questionable impairment ($.39$, $p = .232$). Correspondingly, depression was associated with pain in mild ($.09$, $p = .008$), moderate ($.12$, $p < .001$), and severe ($.06$, $p = .016$) cognitive impairment, but not in those with no/questionable impairment ($.07$, $p = .229$).

4. Discussion

4.1. Discussion

This study confirms the continued existence of the pain-depression dyad in nursing home patients irrespective of cognitive status. Moreover, this study is the first to show that reduced pain intensity is associated with future reduction of depressive symptoms in this population. This is the first large-scale multicentre prospective study investigating the associations between pain and depression over time in nursing home patients at all stages of cognitive impairment, using validated proxy-rated instruments with good validity, reliability, and responsiveness, and controlling for intra-cluster correlation and use of analgesics and/or antidepressants. The obtained OR of depression in patients with moderate to severe pain (unadjusted OR 2.35 , 95% CI 1.76 – 3.12) was similar to results from previous nursing home studies (Cipher and Clifford, 2004; Gruber-Baldini et al., 2005; Leong and Nuo, 2007; Malara et al., 2016; Williams et al., 2005).

Although we found that the association between pain and depressive symptoms was strongest in patients with moderate cognitive impairment (Table 5), the difference in effect between the four stages of cognitive impairment was not significant ($p = .227$). This means that we did not find evidence to suggest that the association changed with increasing severity of cognitive impairment. In patients with no/questionable impairment, the association was nonsignificant, probably because this group was smaller ($n = 49$). Patients with severe cognitive impairment appear to have a weaker association than those with moderate impairment, which did not reach significance despite this group being relatively large ($n = 201$), but the difference in effect was not significant with the current sample size.

At baseline, 48% received one or more analgesics, while 40% still had moderate to severe pain. A previous study found that in 2011, 58%

Table 4
Results from mixed model analyses; unstratified.

Dependent variable	Independent variable	Model 1		Model 2		Model 3		Model 4		Model 5	
		C	p	C	p	C	p	C	p	C	p
CSDD	MOBID-2	.45	< .001*	.48	< .001*	.48	< .001*	.44	< .001*	.44	< .001*
	Time (months)	-.11	.002	-.10	.007*	-.11	.002*	-.11	.003*	-.12	.001*
	MMSE			-.12	< .001*	-.12	< .001*	-.12	< .001*	-.12	< .001*
	Age			-.10	< .001*	-.09	< .001*	-.11	< .001*	-.09	< .001*
	Sex			-.08	.814	-.30	.381	-.13	.711	-.32	.336
MOBID-2	Antidepressants					1.2	< .001*			1.2	< .001*
	Analgesics							.49	.006*	.41	.023*
	CSDD	.09	< .001*	.10	< .001*	.10	< .001*	.09	< .001*	.09	< .001*
	Time (months)	.01	.560	.01	.398	.01	.393	.00	.927	.00	.973
	MMSE			.00	.721	.00	.715	.00	.795	.00	.768
	Age			.02	.014*	.02	.015*	.02	.052	.02	.065
	Sex			.26	.069	.26	.068	.18	.180	.19	.153
	Antidepressants					-.02	.873			-.08	.440
	Analgesics							.65	< .001*	.65	< .001*

Model 1: Association between pain and depression over time, unadjusted; **Model 2:** Association between pain and depression over time, adjusted for cognitive function, age, and sex; **Model 3:** Association between pain and depression over time, adjusted for number of prescribed antidepressants, cognitive function, age, and sex; **Model 4:** Association between pain and depression over time, adjusted for number of prescribed analgesics, cognitive function, age, and sex; **Model 5:** Association between pain and depression over time, adjusted for number of prescribed antidepressants and analgesics, cognitive function, age, and sex. C, coefficient; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale. Analyses include all patients with valid assessments at any time point, and are adjusted for time to follow-up (4/6 months) and intra-cluster effects at the nursing home level.

* Significant association at $p < .05$ level.

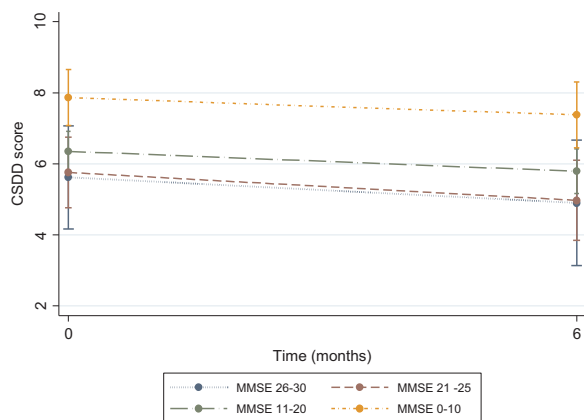


Fig. 2. Mixed model; course of depressive symptoms by cognitive function.

of nursing home residents in Norway were prescribed analgesics (Sandvik et al., 2016b). While we found a lower overall prescription rate, this is probably explained by the large proportion of recently admitted nursing home patients in our sample. In the COSMOS group, which is more comparable to the general nursing home population,

64% received analgesics. This may indicate a slight increase in analgesic use from 2011 to 2014. A higher number of prescribed analgesics at baseline, or an increase in the number of prescribed analgesics from baseline to follow-up, was associated with higher levels of both pain and depression. One explanation for this may be that the prescribed treatment was insufficient to relieve pain effectively. Another possibility is that use of one or more analgesics may increase the total symptom burden due to adverse effects or interactions between analgesics or other psychotropic drugs such as sedatives. Known adverse effects of opioid analgesics in the elderly, such as sedation or reduced appetite (Chau et al., 2008), may also have been reported as symptoms of depression.

At baseline, 38% had depression and 31% received antidepressants. A recent systematic review found that in Western nursing homes from 2004 to present, the use of antidepressants ranged from 18% to 48%, and in the Nordic countries from 39% to 43% (Janus et al., 2016). In the COSMOS sample, 40% used antidepressants, which is consistent with these previous reports. Systematic reviews and meta-analyses have not found clear benefit of antidepressants for moderate to severe depression in people with dementia (Leong, 2014; Nelson and Devanand, 2011), despite this the rate of antidepressant use in nursing home patients appears to remain unchanged (Gulla et al., 2016; Janus et al., 2016). We found that antidepressant use was associated with

Table 5
Mixed model, stratified for level of cognitive impairment.

Dependent variable	Independent variable	MMSE 0–10 (N = 201)		MMSE 11–20 (N = 453)		MMSE 21–25 (N = 115)		MMSE 26–30 (N = 49)		P-value ^a
		Coefficient	p	Coefficient	p	Coefficient	p	Coefficient	p	
CSDD	MOBID-2	.24	.050	.62	< .001*	.47	.005*	.39	.232	.227
	Time (months)	-.08	.322	-.10	.042*	-.13	.156	-.10	.436	.978
	Sex	.72	.392	-.45	.290	-.03	.967	.65	.706	.700
	Age	-.09	.086	-.09	.006*	-.13	.019*	-.11	.284	.830
MOBID-2	CSDD	.06	.016*	.12	< .001*	.09	.008*	.07	.229	.381
	Time (months)	-.06	.161	.04	.033*	.02	.626	.00	.985	.165
	Sex	.49	.126	.09	.612	-.12	.751	1.5	.018*	.024*
	Age	.04	.076	.02	.096	.00	.871	.01	.762	.417

CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale. Analyses include all patients with valid assessments at any time point, adjusted for time to follow-up (4/6 months) and intra-cluster effects at the nursing home level.

* Significant association at $p < .05$ level.

^a P for interaction is a test for difference in effect between the separate groups.

higher levels of depression. Similar results have been reported previously, possibly due to inconclusive efficacy combined with increased likelihood of prescribing to those with severe depressive symptoms (Borza et al., 2015). While the efficacy of antidepressants for depression in people with dementia is uncertain and may be difficult to assess, elderly patients with dementia are also particularly susceptible to adverse effects and drug interactions (Gulla et al., 2016). Increased risks of seizures, falls, fractures, and mortality have been reported in older patients receiving antidepressants (Bakken et al., 2013; Coupland et al., 2011).

The therapeutic benefit of analgesic and antidepressant drugs should be assessed regularly with validated tools, and weighed carefully against potential adverse effects. Future advances should go towards systematic symptom assessment in people with dementia, in order to identify those in need of treatment, and to stop unnecessary or harmful treatment.

4.2. Limitations

This study has its limitations. Due to the observational design of the study, we cannot draw conclusions on causality from this material. Furthermore, the REDIC and COSMOS trials had different inclusion criteria. The REDIC trial, which contributed the majority of our population, included patients at admission to nursing home care. Thus our results may not be directly generalisable to other populations with varying lengths of stay. Nursing home admission is associated with increase of depressive symptoms, which may not be congruent with depressive disorder (Achterberg et al., 2006). However, the persistence rate of depression 6 months after admission has been estimated to 63% (Smalbrugge et al., 2006), which is similar to that found in other studies (Selbaek et al., 2013), and to our observed rate (67%). The proportion of recently admitted patients could also strengthen our results, as the length of stay in nursing home care is typically short. A UK study found that 53% died within 6 months of admission, while a small number of patients stayed much longer, increasing the average stay to 14 months (Kelly et al., 2010). Though time to follow-up differed between the REDIC and COSMOS trials, the mixed model analyses included a time variable to ensure that this did not affect the results. The main analyses (Table 4) were re-calculated separately for each group, with unchanged results. The combined data set enabled us to include a high number of patients, recruited from a wide network of research centres, controlling for possible confounding factors to ensure robustness of results. Some potential sources of confounding remain. The number of scheduled prescriptions for any analgesic or antidepressant was recorded at each time point, but we did not assess the duration of use, appropriateness of the prescribed dose, or changes in the prescribed doses of individual drugs. Nor did we assess any use of as-needed drugs. Furthermore, use of nonpharmacological interventions for either pain or depression was not assessed. While the CSDD scale includes some items that may overlap with pain, such as “multiple physical complaints”, pain was significantly associated with NPI depression, reducing the likelihood that our results are due to symptom overlap.

5. Conclusion

We found highly significant, prospective associations between pain and depression, irrespective of analgesic or antidepressant use. These associations were replicated in groups with mild, moderate, and severe cognitive impairment. Because a reduction in pain was associated with less depressive symptoms, patients with dementia should be regularly assessed for untreated pain. The benefit of analgesic or antidepressant drugs should also be assessed regularly and weighed carefully against the potential for adverse effects.

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